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ETHOSOMES: NOVEL VEHICLE INDRUG DELIVERY

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ABSTRACT

Ethosomesare novel vesicular carriers that effectively and efficiently deliver molecules with different physical and chemical properties across the skin and into deep skin layers. This paper reviews the unique characteristics of the ethosomal carriers, the mechanism of action with a brief note focusing on the work carried out with drugs utilizing ethosomal systems in animal models, in vitro studies and in clinical studies. The paper concludes with a discussion on the challenges/ limitations of the etho some system of drug administration and future directions to overcome the challenges.

KEYWORDS: Ethosomes, Nanodrug Delivery, Nanotechnology, Nanovesicles & Novel Vehicle Transdermal Drug Delivery

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INTRODUCTION

Nano medicine is up-and-coming fields which advocate the combined understanding and techniques of nanotechnology and medical biology. Nano medicine employs materials in nano dimension to aid in diagnosis of diseases and to deliver drugs into specific sites.

The size of nanoparticles used in drug delivery are generally < 100 nm in at least one of the dimensions. They are made of biodegradable materials that may be natural or synthetic polymers.

The nano-drug delivery system to be used is determined based on the physical properties, chemical properties and the pharmacodynamics of the drugs being selected for treatment. Nanoparticles with different compositions and biological properties have been extensively studied for the purpose of drug delivery. To develop an ideal drug delivery device is quite challenging. The key challenges are biocompatibility of the device and delivering the drug without alteration in its efficacy. In spite of the aforementioned challenges, drug delivery system on a nano scale have been developed successfully.

BACKGROUND

Nanoparticles are sought after to be used as vehicles for drug delivery because of two reasons:

- They deliver the drug at the site of disease. This property is called as targeted drug delivery.
- They improve the uptake of poorly soluble drugs.

Targeted Drug Delivery Vs Untargeted Drug Delivery: (Figure 1)

The use of macromolecules to deliver a drug imposes quite a number of challenges. Some of which are instability of the drug in vivo, poor solubility, poor absorption in the body leading to reduced bioavailability of the drug and

possible adverse effects of drugs (1). For that reason using novel drug delivery systems for targeted drug delivery only to the diseased site could be an option to solve these vital issues.

Nano Drug Delivery Systems

The primary goals of nano drug delivery system include:

- Specific drug targeting and delivery.
- Reducing toxic effect of the drug while maintaining the therapeutic dose of the drug.
- Higher biocompatibility and safety.
- Devolopment of new and safer medicines

Drugs that have been delivered using nano systems:

- "Amphotericin B, an anti-fungal drug has been complexed with lipids-based nanotubes with poly alkylcyanoacrylates (PACA) nanoparticles used as a carrier. Amphotericin B in this formulation are targeted directly into macrophages for the treatment of leishmaniasis. (2)
- Doxorubicin an anti- cancer drug bound to polysorbate-coated nanoparticles has been shown to cross the intact blood-brain barrier and be released at therapeutic concentrations in the brain. (3)Other anti-cancer drugs such as paclitaxel, doxorubicin, 5-fluorouracil and dexamethasone have been successfully formulated using nanomaterials".

Various nanoparticles used in drug delivery systems include chitosan, alginate, gelatin, cellulose, hydrogels, xanthum gum, liposomes, polymeric micelles, dendrimers, ethosomes, nanocrystals and polymer carriers such as polylactic acid and polycaprolactone.

ETHOSOMES

Ethosomes dates back to the 90's and was developed by Touitou *et al* in the year1997. Ethosomes are nano vesicles used for dermal and transdermal delivery of the drug molecules. They are made out of ethanol, phospholipids, and water. The reason for usingethanol is that it is reported to be a very efficient in permeating the epithelium of skin by affecting the intercellular region of the stratum corneum. Ethosomes are soft, flexible and pliable nano vesicles designed to be non invasive carriers that not only enable drugs to reach deep layers of the skin but also the drugs can enter the systemic circulation. (4)

Mechanism of Action of Ethosomes(5)

The mechanism by which drugs are delivered can be attributed to the interaction between ethosomes and skin lipids. A possible mechanism for this interaction has been proposed. In the proposed mechanism the action of ethosomes have been divided into two phases. The first part is called as 'Ethanol effect' and the second part is called as 'Ethosome effect'. A detailed discussion of the mechanism of action of ethosomes is given below.

Ethanol Effect

"The first part of the mechanism of ethosome is called the ethanol effect. As the name suggest the agent responsible for this first phase of penentration is ethanol. Here ethanol has been shown to interact with the lipid molecules in the

polar head group region of the stratum corneum (the outermost layer of the skin). This results in a reduction in the transition temperature of the lipids in the stratum corneum. When there is a reduction in the transition temperature there is an increase in the fluidity of the lipid molecules. This in turn decreases the density of the lipid layer of the skin".

Ethosome Effect

"The ethanol effect is followed by the ethosome effect, which is the second part of penetration. Ethosome effect includes permeation and penetration of the lipid layer by the ethosomal nano vesicle. This occurs by the fusion of the ethosomes with lipids that have loosened because of the ethanol effect. Once the ethosomes reach the deeper layers of the skin they release the drug by disintergration of the nano vesicle.

Apart from interaction of the ethosome with the lipid molecules in the stratum corneum, ethanol also makes the vesicles with soft and flexible, which allow them to penetrate more easily into the skin. Finally the drug is release at various points along the penetration pathway followed by transdermal absorption".

Methods of Preparation of Ethosomes

Different methods for the preparation of ethosomes have been reported in reported. Each procedure has its own advantages, disadvantages and challenges in preparation. Some commonly used methods have been discussed.

The primary/ basic composition of ethosomes are ethanol, phospholipids and water.

- **Classic Method: (6)**

  "In this method the and drug to be delivered is dissolved in a solvent (i.e) ethanol along with phospholipid. This is heated to 30°C±1°C in a water bath and a fine stream of double distilled water is added to the lipid mixture. This is accompanied with constant stirring of the mixture at 700 rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles".

- **Hot Method: (7)**

  "In this technique the drug is first dissolved in a mixture of ethanol and propylene glycol. The mixture is then added to a phospholipid dispersion in water at 40°C. After thorough mixing, the preparation is sonicated at 4°C for three cycles. Each cycle lasts for five minutes, with a rest of five minutes between each cycle. Sonication is done using the Probe Sonicator. The formulation is then homogenized pressure using a high pressure homogenizer at 15,000 psi to get nano-sized ethosomes".

- **Cold Method: (8)**

  "In this method the drugwith phospholipids and other lipid materials are dissolved in ethanol in a covered vessel at room temperature. It is vigorously stirred to ensure proper mixing. The mixture is then heated up to 30°C in a water bath. To this mixture, water heated to 30°C in separate vessel is added and stirred for five minutes. This results in the formation of vesicles. The size of the vesicles can be reduced if needed by using a sonicator or by extrusion. Finally the formulation is properly stored under refrigeration. This step is very important to maintain the integrity of the formed vesicles".

- **Classic Mechanical Dispersion Method: (9)**

  "In the mechanical dispersion technique soya phosphotidylcholine is used. Soya phosphotidylcholine is dissolved in a mixture of chloroform and methanol taken in the ratio of3:1(3 parts of chloroform: 1 part of methanol) in round bottom flask. Thesolvents are removed using rotary vacuum evaporator at a temperature above the lipid transition temperature. This forms a thin lipid film on wall of the flask. Finally, anytraces of solvent mixture deposited on the lipid film are removed by leaving the contents under vaccum overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the flask at suitable temperature. Ethosomes are formed on the surface of the flask".

  There is no ideal technique that is available to construct ethosomes, although a lot of techniques are available. Any technique can be chosen based on the available resources and materials.

Types of Ethosomal Formulations: (10)

Classical Ethosomes

"Classical ethosomesare composed of phospholipids and high concentration of ethanol up to 45% w/w and water. Classical ethosomes are reported to be more efficient thanliposomes for transdermal delivery of drugs because they are smaller in size and has negative zeta- potential (potential difference between a solid and a liquid) which give ethosomes higher entrapment efficiency".

Binary Ethosomes

"Binary ethosomes are basically classical ethosomes with a slight modification. Binary ethosomes are prepared by adding other types of alcohol to the classical ethosomes. The most commonly used alcohols in the preparation of binary ethosomes are propylene glycol and isopropyl alcohol".

Transethosomes

"Transethosomes are the latest generation of ethosomal systems. Transethosomes were first developed reported by Song *et al* in the year 2012. Components of the basic classical ethosomes are present in transethosomes. Apart from that they contain some additional compound such as a penetration enhancer or a surfactant. Transethosomes were developed in an attempt to incorporate classical ethosomes with deformable liposomes (transfersomes) into a single formula. Transethosomes have superior properties than classical ethosomes in terms of penetration efficacy and biocompatibility".

Drugs that have been Delivered using Ethosomal Delivery System

Animal Studies

- Ainbinder and Touitou in an animal study on rabbits compared the skin penetration potential of ethosomal testosterone (Testosome) with a commercially available transdermal patch of testosterone. Results from the study showed that testosterone from the ethosomal formulation had almost 30 times higher skin permeation when compared to the transdermal patch. (11)
- Lodzki *et al* prepared an ethosomal formulation ofCannabidiol(CBD). Cannabidiol is a drug used for the treatment of rheumatoid arthritis and has anti-inflammatory action. The drug, CBD- ethosomal formulation was topically applied on mice. Results from the study show that encapsulation of CBD in ethosomes significantly

increased the skin permeation and accumulation in plasma. In doing so there is an increase in the biological availability and activity of the drug. (12)

- Mishra *et al* evaluated the efficiency of ethosomal formulation for transcutaneous immunization against Hepatitis B. HBsAg-loaded ethosomes are able to generate a strong immune response by traversing the skin and targeting the immunological milieu of the skin. (13)

In-vitro Studies

Esposito *et al* conducted an invitro study to compare ethosomal formulation and liposomal formulation of azelaic acid. Azelaic acid is an anti-keratinizing agent used in the treatment of acne. 200nm and 400nm of ethosome with the drug azelaic acid were prepared as a topical vehicle. The drug release and kinetics comparing ethosomal formulation and liposomal formulation were studied and compared. Results from the study demonstrated that the drug release rate was more rapid from ethosomal drug formulations than from liposomal formulations. (14)

Human Trials

Paolino *et al* investigated the efficacy of ethosomes for dermal delivery of ammonium glycyrrhizinate. Ammonium glycyrrhizinateis a drug that is used for the treatment of a range of inflammatory skin diseases. The study was done in human volunteers. Ethosomal formulation of the drug that was applied topically showed excellent skin tolerability for 48-hours after application. The biological anti-inflammatory action was also much superior in case of ethosomal formulation as compared to ethanolic or aqueous solution of the drug. (15)

Commercially available Ethosomal Formulations

- "OsmoticsInc an American company markets an anti- cellulite cream called Lipoduction. Lipoduction has been formulated with the use ofethosomal technology. It has been reported that this formulation penetrate the skin lipid barrier to delivered the drug directly into the fat cells and improved the appearance of cellulite by up to 80% in less than 60 days. (16)
- **Nanominox:** First minoxidil-loaded ethosomes product. Contains 4% minoxidil.
- **Supravir Cream:** It is a formulation of acyclovir for the treatment of herpes virus. It has a long shelf life and the drug was stable for at least three years at 25°C. Skin permeation experiments showed that this cream retained its penetration enhancing properties even after three years".(17).

Advantages of Ethosomes as Drug delivery Device

- "Improved permeation of drug through skin for transdermal drug delivery. It is an easy method for transdermal drug delivery in comparison to other complicated methods like iontophoresis and phosphophoresis.
- Delivery of large molecules such as peptides, protein molecules and hormones is made possible.
- Excellent patient compliance as the ethosomal drug is administrated as a gel or cream.
- Ethosomal vesicles are made of biocompatible non-toxic formulation.
- Ethosomal drug delivery system can be used widely in veterinary and cosmetic fields".

Disadvantages /Limitations of Ethosomes

- Maintaining the stability of the ethosome is challenging. The components undergo oxidative degradation.
- Ethosomes are physically unstable when sterilized.
- Manufacturing of ethosomesmay be expensive.
- Kinetics of the drug cannot be controlled.

FUTURE DIRECTIONS

The exact mechanismby which of intact vesicle permeate across the stratum corneum is not yet fully understood. The process of deformation of the vesicle and the splitting of intact vesicles into the deep layers of the epidermis still remains to be elucidated. More research is needed in this area to improve the properties of the ethosomes.

CONCLUSIONS

Ethosomes have also been proved to be interesting delivery systems for pharmaceutical and cosmetic products. Topically applied ethosomes have been found to be more stable than liposomal formulations. Overcoming the challenges faced in ethosomal formulation such as its oxidative degradation and physical instability would help to deliver more drugs using ethosomes.

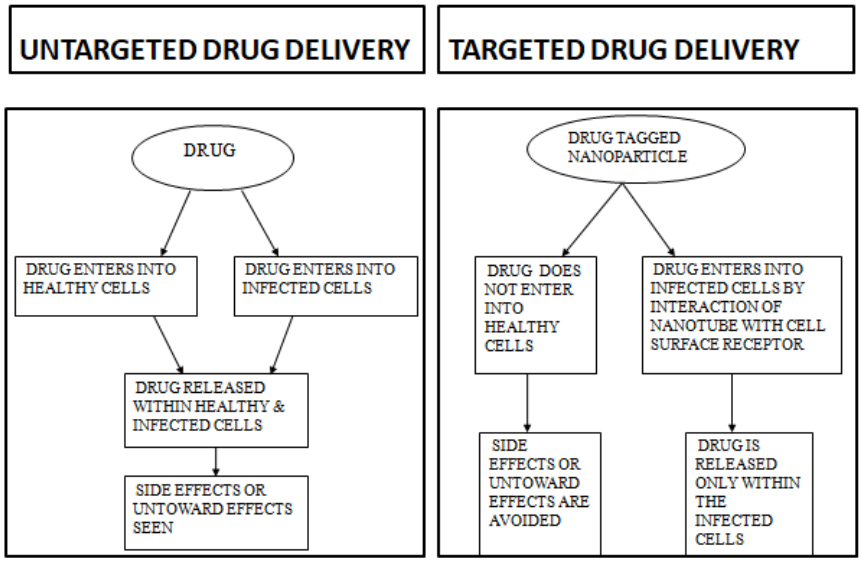

Figure 1: Difference between untargeted and Targeted Drug Delivery.

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